SUNWAY UNIVERSITY

Making Sense of the Different Modes of Supramolecular Association Occurring in Molecular Crystals

Edward R.T. Tiekink
Research Centre for Crystalline Materials

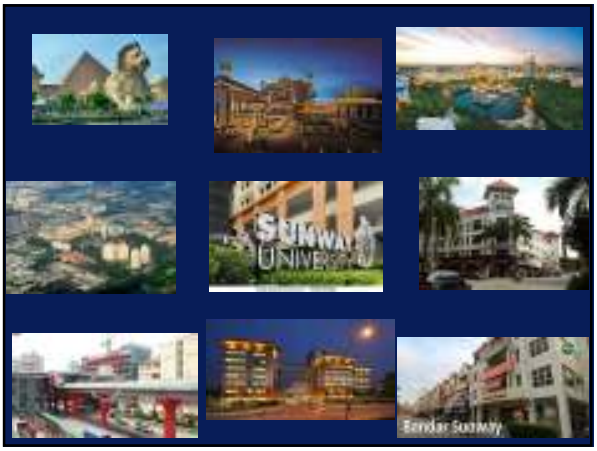
IIt International Conference on
"Crystal Engineering: From Molecule to Crystal" (ICE-FMC 2019)
30th - 31st March 2019

SUNWAY

Sunway Group

1974: tin-mining

Plantation/Property and Construction, Health, Leisure, Education, Travel and Hospitality



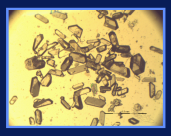
Sunway University

Fortuna Eruditis Favet ("*Fortune favours the prepared mind*")

Crystals?

Why do crystals form?

How do crystals form?



Crystal Engineering

- Determine how Molecules pack
- Design specific architectures
- Optimise for applications

Intermolecular Interactions

Well known, understood and utilised…

Hydrogen-bonding (HB)

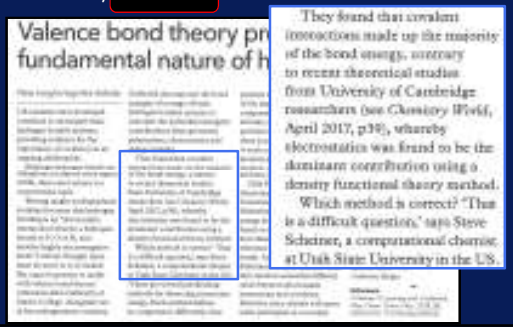
$D—H\cdots A$ (δ^+ on H, δ^- on A)

Intermolecular Interactions

Well known, understood and utilised…

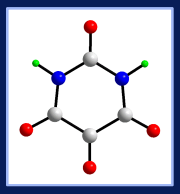
Intermolecular Interactions

Well known, understood and utilised…

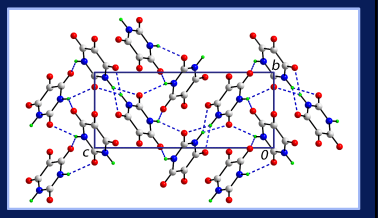


Alloxan

Neutron diffraction: 45 K



2-fold symmetry

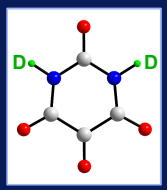


$P4_12_12$

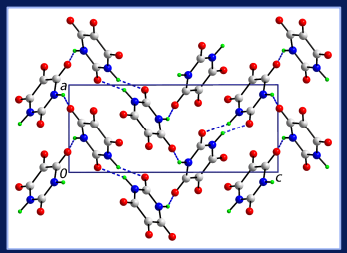
Bifurcated: N···O = 3.15 & 3.22 Å
cf. ΣvdW = 3.07 Å

Alloxan

Phase change < 35 K: $P2_12_12_1$



No symmetry



N···O = 3.11 & 2.99 Å
cf. ΣvdW = 3.07 Å

320

Acta Cryst. (1998). **B54**, 320–329

Carbonyl–Carbonyl Interactions can be Competitive with Hydrogen Bonds

FRANK H. ALLEN,[a]* CHRISTINE A. BAALHAM,[a] JOS P. M. LOMMERSE[a] AND PAUL R. RAITHBY[b]

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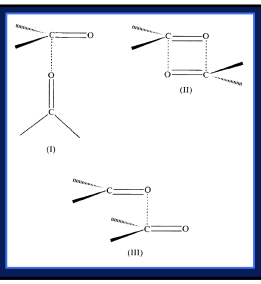
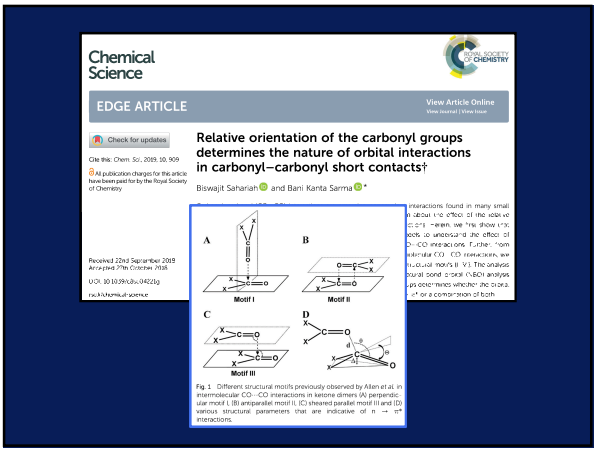
(Received 25 September 1997; accepted 22 January 1998)





Chemical Science

EDGE ARTICLE

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Relative orientation of the carbonyl groups determines the nature of orbital interactions in carbonyl–carbonyl short contacts†

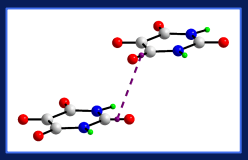
Biswajit Saharian and Bani Kanta Sarma*

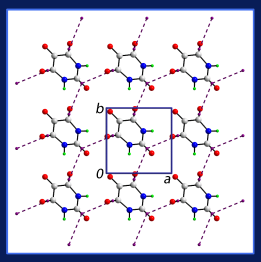
Motif I Motif II Motif III

Fig. 1 Different structural motifs previously observed by Allen et al. in intermolecular CO···CO interactions in ketone dimers (A) perpendicular motif I, (B) antiparallel motif II, (C) sheared parallel motif III and (D) various structural parameters that are indicative of n → π* interactions.

Alloxan

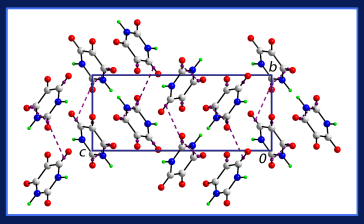
Neutron diffraction : 45 K





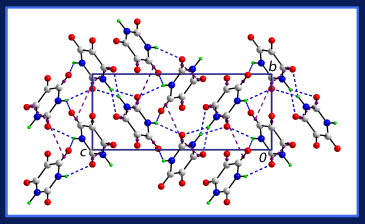
Alloxan

Neutron diffraction: 45 K



Alloxan

Neutron diffraction: 45 K



Alloxan

HIGHLIGHT www.rsc.org/crystengcomm | CrystEngComm

Alloxan: Is it really a problem structure?

Jack D. Dunitz* and W. Bernd Schweizer*

DOI: 10.1039/b704754c

For more than forty years the crystal structure of alloxan with its remarkable stability and unusually high melting point but its absence of "conventional" hydrogen bonds has been regarded as problematic. Now that intermolecular cohesive energies can be calculated with reasonable accuracy, the stability of the alloxan structure is seen to fit in well with that of other isostructural compounds. The problem can be regarded as solved or rather as non-existent.

Alloxan

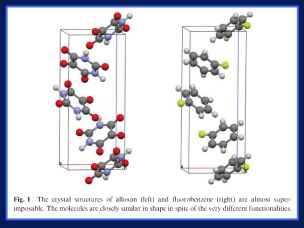


Fig. 1 The crystal structures of alloxan (left) and fluorobenzene (right) are almost superimposable. The molecules are closely similar in shape in spite of the very different functionalities.

Table 1 Unit cell dimensions of alloxan and several isostructural crystals with space group $P4_12_12$ (or equivalently $P4_32_12$)

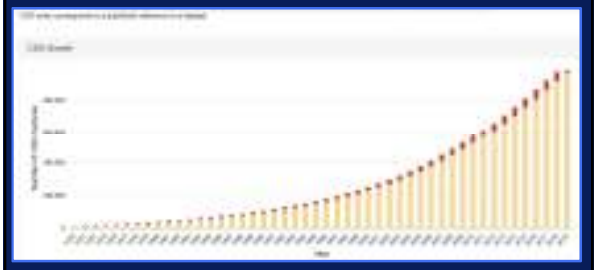
	$a = b$/Å	c/Å
Alloxan[5]	5.841	13.853
Fluorobenzene[13]	5.799	14.503
Pyridinium fluoride[14]	6.059	14.280
Pyridine-N-oxide[15]	5.816	13.747
Benzonitrile[16]	6.361	14.240
Cyclopentene-1,2,3-trione[17]	5.701	14.113
Borazine[18]	5.428	16.279
Benzene (virtual structure N5)[19]	5.54	15.32
Benzene (virtual structure H2)[18]	5.29	14.29

The importance of global molecular packing

…most organic molecules feature hydrogen atoms at the periphery and so that C–H···X interactions are inevitable

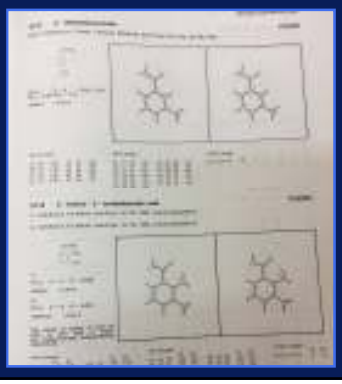
Chem. Soc. Rev., **2009**,*38*, 2622-2633

Cambridge Structural Database



Cambridge Structural Database

Cambridge Structural Database



Prevalence of Space Group Adoption

CSD: 865,342 entries

$P2_1/c$	279041	34.5
$P\bar{1}$	198014	24.7
$C2/c$	67434	8.4
$P2_12_12_1$	58438	7.2
$P2_1$	41791	5.2
$Pbca$	26951	3.3

Six close-packing SG's account for >83% of structures

"Egg Causality Dilemma"

"Hydrogen Bonding and Co-crystal Technology"

FEATURE ARTICLE

Designer crystals: intermolecular interactions, network structures and supramolecular synthons

Gautam R. Desiraju

School of Chemistry, University of Hyderabad, Hyderabad 500 046, India

Questions relating to the prediction of the crystal structure or structures of a given organic molecule may be more gainfully reversed so that retrosynthetic analysis of a target crystal network leads to the identification of molecular precursors. Crystal engineering is solid state supramolecular synthesis and supramolecular synthons, units formed by synthetic operations involving intermolecular interactions, may be used to focus efforts in such logic-driven retro-synthesis.

molecular structure of an organic substance, what is its crystal structure?' The molecular basis of organic chemistry makes such a question seem almost intuitive and much progress was made and is continuing to be made in seeking answers here. The first well-documented attempt in this direction is the correlation, established in 1951 by the great chemical crystallographer J. Monteath Robertson, between the molecular structures of planar fused-ring aromatic hydrocarbons and their packing type as revealed by the crystallographic short axis.[7] Robertson divided such hydrocarbons into two rather broad but fairly

"Caveat"

CMC

Systematic analysis of the probabilities of formation of bimolecular hydrogen-bonded ring motifs in organic crystal structures

Frank H. Allen,*[a] W. D. Samuel Motherwell,[a] Paul R. Raithby,[b] Gregory P. Shields[a,b] and Robin Taylor[a]

[a] *Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK CB2 1EZ. E-mail: allen@ccdc.cam.ac.uk*

[b] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW*

Received (in Cambridge, UK) 15th September 1998, Accepted 5th November 1998

A methodology has been developed for characterising hydrogen-bonded ring motifs formed between two organic molecules without any prior knowledge of the topology or chemical constitution of the motifs. The method has been implemented by modifying the current Cambridge Structural Database (CSD) System programs. All intermolecular ring motifs comprising ≤20 atoms formed with N—H···N, N—H···O, O—H···N and O—H···O hydrogen bonds in organic structures in the CSD have been classified. The 75 bimolecular motifs occurring in >12 structures in the CSD are described in terms of their graph sets and chemical functionalities. Motifs are ranked according to their frequency of occurrence and according to their probabilities of formation, *i.e.* their frequency relative to the number of possible motifs which could have formed. These probabilities provide insights into the relative robustness of known and potential supramolecular synthons.

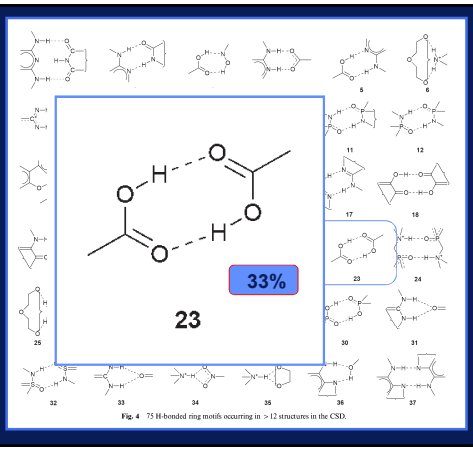
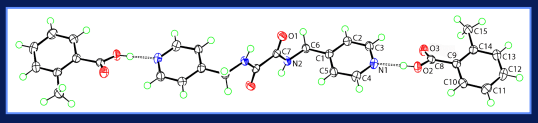
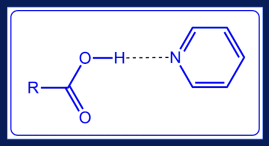


Fig. 4 75 H-bonded ring motifs occurring in > 12 structures in the CSD.

Co-crystals: Non-covalent derivatisation





{C(=O)OH...N(py)} heterosynthon

Reliable

98% formation in the absence of competition

CrystEngComm

COMMUNICATION

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Accepted 28th September 2018

DOI: 10.1039/c8ce01492b

rsc.li/crystengcomm

Co-crystallization of anti-inflammatory pharmaceutical contaminants and rare carboxylic acid–pyridine supramolecular synthon breakdown†

Qixuan Zheng, Samantha L. Rood, Daniel K. Unruh and Kristin M. Hutchins*

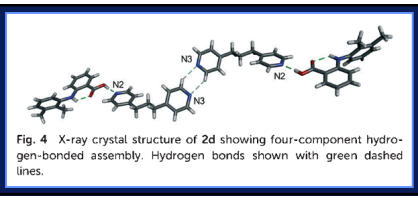


Fig. 4 X-ray crystal structure of **2d** showing four-component hydrogen-bonded assembly. Hydrogen bonds shown with green dashed lines.

research communications

CRYSTALLOGRAPHIC COMMUNICATIONS

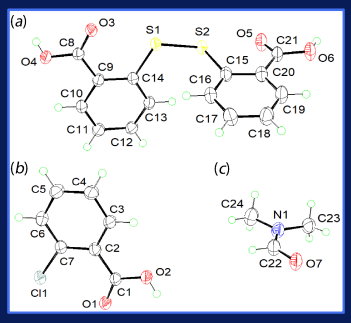
ISSN 2056-9890

A 1:1:1 co-crystal solvate comprising 2,2′-dithiodibenzoic acid, 2-chlorobenzoic acid and *N*,*N*-dimethylformamide: crystal structure, Hirshfeld surface analysis and computational study

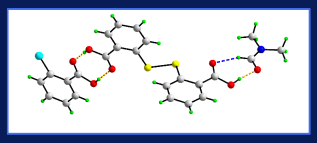
Sang Loon Tan and Edward R. T. Tiekink*

Received 6 March 2019
Accepted 19 March 2019

Research Centre for Crystalline Materials, School of Science and Technology, Sunway University, 47500 Bandar Sunway, Selangor Darul Ehsan, Malaysia. *Correspondence e-mail: edwardt@sunway.edu.my



-73.2 kJ/mol



-45.9 kJ/mol

450 structures with RCO_2H and DMF

200 have hydrogen bonding between RCO_2H and DMF

40% probability

Intermolecular Interactions

Well known…

Hydrogen-bonding (HB)
Halogen-bonding (HB)

$A-H\cdots B$ (δ^+ δ^-)

$A-X\cdots B$ (δ^- δ^-)

CHEMICAL REVIEWS

Review

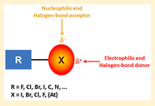
pubs.acs.org/CR

The Halogen Bond

Gabriella Cavallo,[†] Pierangelo Metrangolo,[*,†,‡] Roberto Milani,[‡] Tullio Pilati,[†] Arri Priimagi,[§] Giuseppe Resnati,[*,†] and Giancarlo Terraneo[†]

[†]Laboratory of Nanostructured Fluorinated Materials (NFMLab), Department of Chemistry, Materials and Chemical Engineering "Giulio Natta", Politecnico di Milano, Via L. Mancinelli 7, I-20131 Milano, Italy
[‡]VTT-Technical Research Centre of Finland, Biologinkaja 7, 02150 Espoo, Finland
[§]Department of Chemistry and Bioengineering, Tampere University of Technology, Korkeakoulunkatu 8, FI-33101 Tampere, Finland

ABSTRACT: The halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity. In this fairly extensive review, after a brief history of the interaction, we will provide the reader with a snapshot of where the research on the halogen bond is now, and, perhaps, where it is going. The specific advantages brought up by a design based on the use of the halogen bond will be demonstrated in quite different fields spanning from material sciences to biomolecular recognition and drug design.

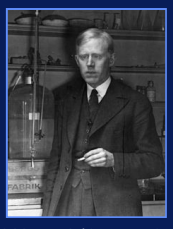


Intermolecular Interactions

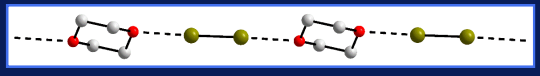
Well known…

Hydrogen-bonding (HB)
Halogen-bonding (HB)

"…for their contributions to the development of the concept of conformation and its application in chemistry."



Odd Hassel (1897 – 1981)



Halogen-bonding

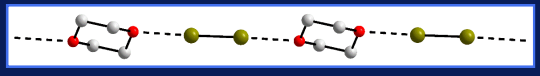
Halogen-bond acceptor Nucleophilic

δ^-

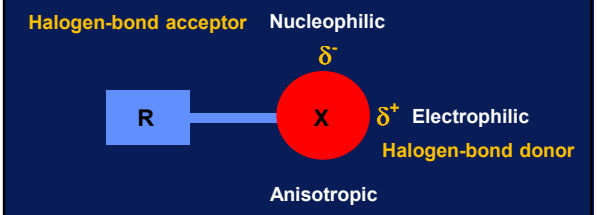
R — X δ^+ Electrophilic

Halogen-bond donor

Anisotropic

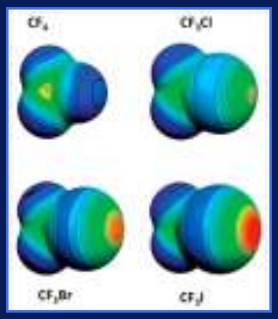


Halogen-bonding



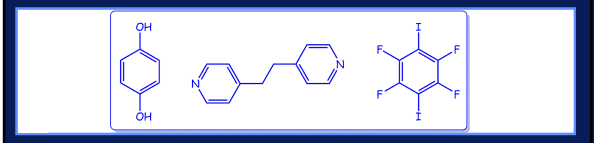
Polar cap, σ-hole

σ-hole

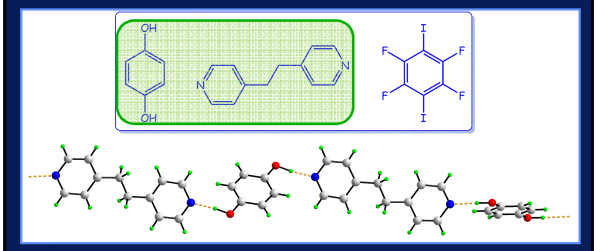


Clark, T.; Hennemann, M.; Murray, J. S.; Politzer, P.
Halogen Bonding: The Sigma-Hole *J. Mol. Model.* **2007**, *13*, 291– 296

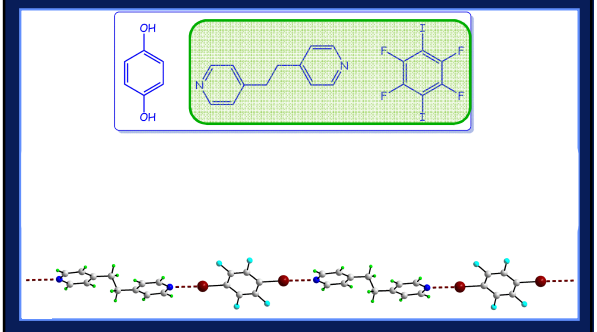
Hydrogen Bonding versus Halogen Bonding



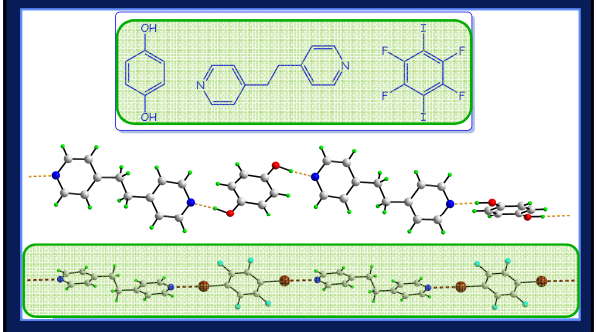
Hydrogen Bonding versus Halogen Bonding



Hydrogen Bonding versus Halogen Bonding



Hydrogen Bonding versus Halogen Bonding



Intermolecular Interactions

Well known…

Hydrogen-bonding (HB)
Halogen-bonding (HB)

$D-H\cdots A$ (δ^+ δ^-)

$D-X\cdots A$ (δ^- δ^-)

$(HB)^2$: Similar in energy = 5 – 15 kcal/mol

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Cite this: Chem. Commun., 2019, 55, 2380

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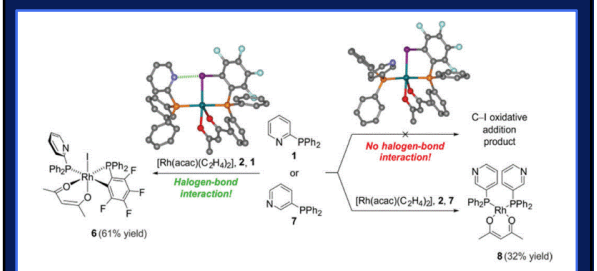
DOI: 10.1039/c8cc08884e

rsc.li/chemcomm

Halogen bonding effects on the outcome of reactions at metal centres†‡

Lucas Carreras, Jordi Benet-Buchholz, Antonio Franconetti, Antonio Frontera, Piet W. N. M. van Leeuwen and Anton Vidal-Ferran



Scheme 4 Reactivity of 2-iodo-3,4,5,6-tetrafluorophenyldiphenylphosphine **2** and $[Rh(acac)(C_2H_4)_2]$ with 2-pyridyldiphenylphosphine **1** and 3-pyridyldiphenylphosphine **7**.

Molecular packing

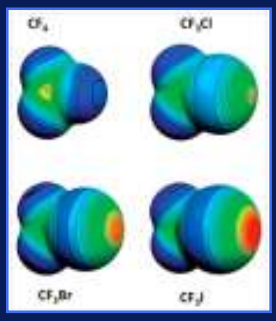
Well known…

Hydrogen bonding
Halogen bonding

"Emerging"

Secondary bonding
M···M interactions
M···H interactions
Interactions involving chelate rings

σ-hole



Halogen bonding

Chalcogen bonding

Pnicogen bonding

Tetrel bonding

Aerogen bonding

Clark, T.; Hennemann, M.; Murray, J. S.; Politzer, P.
Halogen Bonding: The Sigma-Hole *J. Mol. Model.* **2007**, *13*, 291– 296

…favorable noncovalent interaction between a covalently bonded atom of Group 18 (known as noble gases or aerogens) and a negative site, for example, a lone pair of a Lewis base or an anion.

Faraday Discussions
Cite this: *Faraday Discuss.*, 2017, 203, 93
PAPER
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Intermolecular interactions in molecular crystals: what's in a name?

Alison J. Edwards, [a] Campbell F. Mackenzie, [b]
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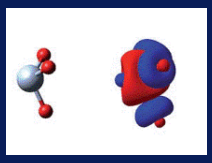

isosurfaces of the deformation electron density

Repackaging:

Tetrel, pnictogen and chalcogen bonds

Electrophilic sites from Groups 14, 15 & 16, resp.

SECONDARY BONDING TO NONMETALLIC ELEMENTS

N. W. Alcock
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International Edition: DOI: 10.1002/anie.201812132
German Edition: DOI: 10.1002/ange.201812132

*Mitchell A. Nascimento, Elodie Heyer, Joshua J. Clarke, Hugh J. Cowley, Antonio Alberola, Nadia Stephaniuk, and Jeremy M. Rawson**

Abstract: *Formation of radical-radical cocrystals is an important step towards the design of organic ferrimagnets. We describe a simple approach to generate radical-radical cocrystals through the identification and implementation of well-defined supramolecular synthons which favor cocrystallization over phase separation. In the current paper we implement the structure-directing interactions of the E···E bond (E = S, Se) of dithiadiazolyl (DTDA) and diselenadiazolyl (DSDA) radicals to form close contacts to electronegative groups. This is exemplified through the preparation and structural characterization of three sets of radical cocrystals; the 2:2 cocrystal [PhCNSSN]$_2$[MBDTA], (**4**) [MBDTA = methyl benzothiadiazolyl] and the 2:1 cocrystals [C_6F_5CNEEN]$_2$[TEMPO] (E = S, **5**; E = Se, **6**). In **4** the two types of radical are linked via bifurcated inter-dimer $^{[1]}$S···N$^{\bullet}$ interactions whereas **5** and **6** exhibit a set of five-centre $^{[2]}$E···O$^{\bullet}$ contacts (E = S, Se).*

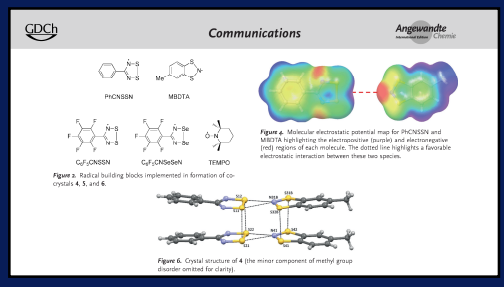


Figure 2. Radical building blocks implemented in formation of co-crystals 4, 5, and 6.

Figure 4. Molecular electrostatic potential map for PhCNSSN and MBDTA highlighting the electropositive (purple) and electronegative (red) regions of each molecule. The dotted line highlights a favorable electrostatic interaction between these two species.

Figure 6. Crystal structure of 4 (the minor component of methyl group disorder omitted for clarity).

ChemPubSoc Europe
DOI: 10.1002/chem.201805131
CHEMISTRY A European Journal Full Paper

Chalcogen Bonding

Non-Classical Synthons: Supramolecular Recognition by S···O Chalcogen Bonding in Molecular Complexes of Riluzole

Sajesh P. Thomas,*[a, b, c] Vijith Kumar,[a, d] Khidhir Alhameedi,[c] and T. N. Guru Row*[a]

Dedicated to Dr. Kuppuswamy Nagarajan on the occasion of his 88th birthday

Abstract: Classical examples of supramolecular recognition units or synthons are the ones formed by hydrogen bonds. Here, we report the ubiquity of a S–O chalcogen bonded synthon observed in a series of supramolecular complexes of the amyotrophic lateral sclerosis drug riluzole. Although the potential of higher chalcogens such as Se and Te to form robust and directional chalcogen bonded motifs is known, intermolecular sulfur chalcogen bonding is considered to be weak owing to the lower polarizability of S atoms. Here, the robustness and electronic nature of a S–O chalcogen bonding non-classical synthon, and the origin of its exceptional directionality have been explored. Bond orders of the drug-coformer chalcogen bonding are found to be as high as one third of a single bond, and they are largely ionic in nature. The contribution of the S–O chalcogen bonded motifs to the lattice energies of a series of crystals from the Cambridge Structural Database has been analyzed, showing they can be indeed significant, especially in molecules devoid of strong hydrogen bond donor groups.

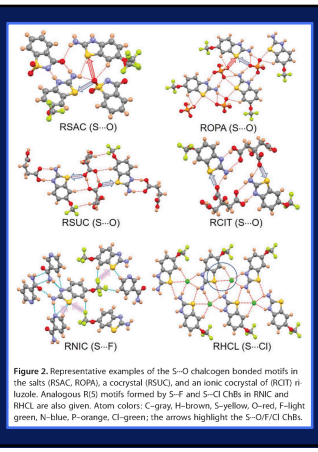


Figure 2. Representative examples of the S···O chalcogen bonded motifs in the salts (RSAC, ROPA), a cocrystal (RSUC), and an ionic cocrystal of (RCIT) riluzole. Analogous R(5) motifs formed by S···F and S···Cl ChBs in RNIC and RHCL are also given. Atom colors: C–gray, H–brown, S–yellow, O–red, F–light green, N–blue, P–orange, Cl–green; the arrows highlight the S···O/F/Cl ChBs.

ChemPubSoc Europe
DOI: 10.1002/chem.201805112
CHEMISTRY A European Journal Full Paper

DNA

Dehalogenation of Halogenated Nucleobases and Nucleosides by Organoselenium Compounds

Santanu Mondal and Govindasamy Mugesh*[a]

Abstract: Halogenated nucleosides, such as 5-iodo-2′-deoxyuridine and 5-iodo-2′-deoxycytidine, are incorporated into the DNA of replicating cells to facilitate DNA single-strand breaks and intra- or interstrand crosslinks upon UV irradiation. In this work, it is shown that the naphthyl-based organoselenium compounds can mediate the dehalogenation of halogenated pyrimidine-based nucleosides, such as 5-X-2′-deoxyuridine and 5-X-2′-deoxycytidine (X = Br or I). The rate of deiodination was found to be significantly higher than that of the debromination for both nucleosides. Furthermore, the deiodination of iodo-cytidines was found to be faster than that of iodo-uridines. The initial rates of the deiodinations of 5-iodocytosine and 5-iodouracil indicated that the nature of the sugar moiety influences the kinetics of the deiodination. For both the nucleobases and nucleosides, the deiodination and debromination reactions follow a halogen-bond-mediated and addition/elimination pathway, respectively.

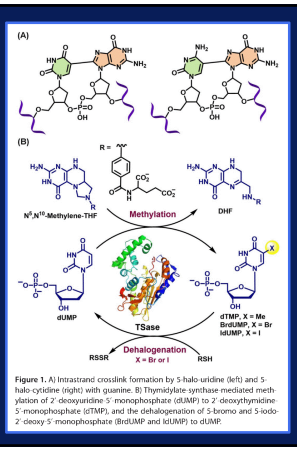


Figure 1. A) Intrastrand crosslink formation by 5-halo-uridine (left) and 5-halo-cytidine (right) with guanine. B) Thymidylate-synthase-mediated methylation of 2′-deoxyuridine-5′-monophosphate (dUMP) to 2′-deoxythymidine-5′-monophosphate (dTMP), and the dehalogenation of 5-bromo and 5-iodo-2′-deoxy-5′-monophosphate (BrdUMP and IdUMP) to dUMP.

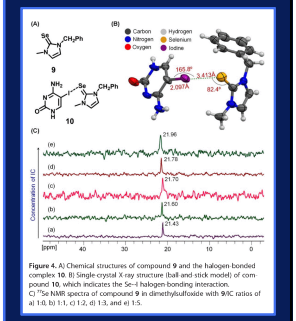
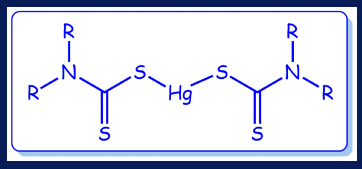


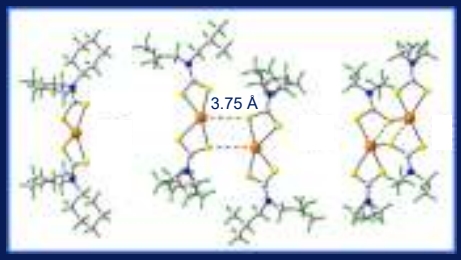
Figure 4. A) Chemical structures of compound **9** and the halogen bonded complex **10**. B) Single crystal X-ray structure (ball and stick model) of compound **10**, which indicates the Se–I halogen bonding interaction. C) ^{77}Se NMR spectra of compound **9** in dimethylsulfoxide with **9**/IC ratios of a) 1:0, b) 1:1, c) 1:2, d) 1:3, and e) 1:5.

Steric Effects and Secondary Bonding



"$Hg(S_2CNR_2)_2$"

Steric Effects and Secondary Bonding

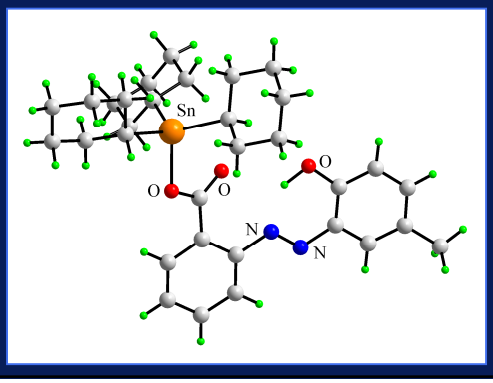


"$Hg(S_2CNR_2)_2$"

Sum of the van der Waals radii for Hg and S = 3.35 Å

increasing size of R

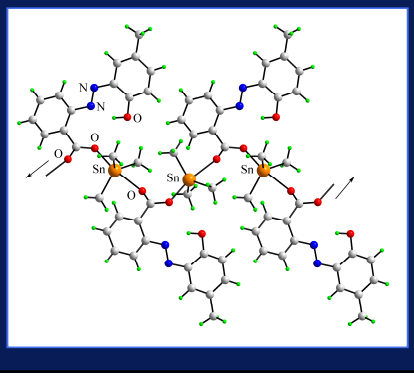
$Cy_3Sn(O_2CR')_2$



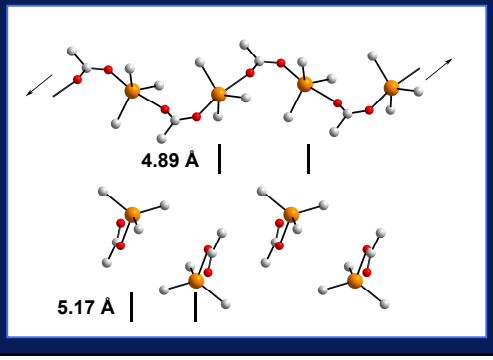
Systematic analysis of $R_3Sn(O_2CR')$

R	^{117}Sn solution	^{117}Sn solid-state
Cy	-8.5	23.7
Me	24.7	148.1

$Me_3Sn(O_2CR'')$



$R_3Sn(O_2CR'')$



Tetrel Bonding: Energy


THE JOURNAL OF PHYSICAL CHEMISTRY A

Article

pubs.acs.org/JPCA

Systematic Elucidation of Factors That Influence the Strength of Tetrel Bonds

Steve Scheiner*

Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322-0300, United States

$(HB)^2$: Similar in energy = 5 – 15 kcal/mol

T = C, Si, Ge & Sn

n = 0	0.9 kcal/mol
n = 1*	6 – 9 kcal/mol
SnF_4	25.5 kcal/mol

Gold Chemistry

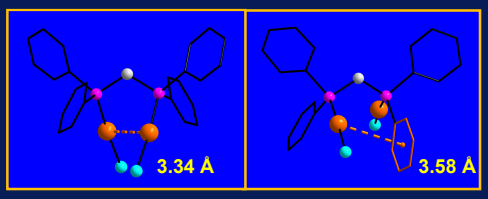
Competition between

i) Au···Au and hydrogen-bonding

Comparable in energy to HB

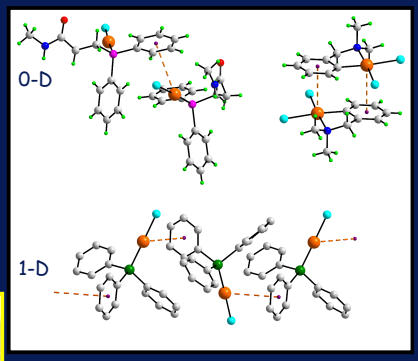
Schmidbaur, *Nature* **413** (2001) 31.

Polymorphs of $(dppm)(AuCl)_2$



Schmidbaur *et al. Chem. Ber.* **110** (1977) 1748;
Healy, *Acta Crystallogr. E* **59** (2003) m1112.

Intermolecular Au···π(arene) interactions



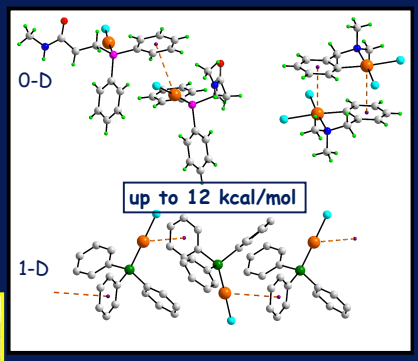
CrystEngComm **11** (2009) 1176; *Gold Bull.* **46** (2013) 81.

PLATON output:

```
Ring-Metal Interactions with Cg-Me <   4.0 Ang.
=============================================================================================================

Cg(I) Res(I)   Me(J)    [    ARU(J)]  Cg(I)-Me(J) Me_Perp    Beta

Cg(1)  [ 1]  -> Au      [  1555.01]      3.263     3.010    22.72
Cg(1)  [ 1]  -> Au      [  3675.01]      3.263    -3.010    22.72

[  1555] = X,Y,Z
[  3675] = 1-X,2-Y,-Z

The Cg(I) refer to the Ring Centre-of-Gravity numbers given in () in the Ring-Analysis above

Cg(I)            x             y             z                Xo            Yo            Zo

Cg(1)        0.5000(3)     1.00000(15)    0.00000(8)          3.4422(18)    11.6056(18)    0.0000(14)
```

cf. sum of the van de Waals radii
= 1.66 + 1.85 = 3.51 Å

Intermolecular Au···π(arene) interactions



RSC Advances **5** (2015) 41401.

Gold Chemistry

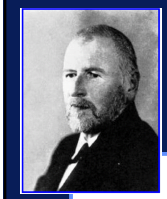
Competition between

i) Au···Au and hydrogen bonding

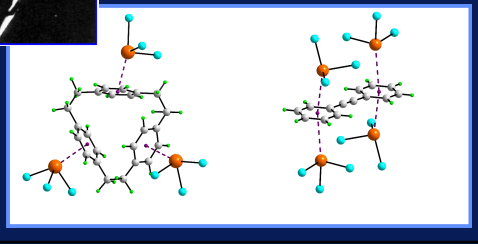
ii) Au···Au and Au···π(arene)

$(HB)^2$: Similar in energy = 5 – 15 kcal/mol

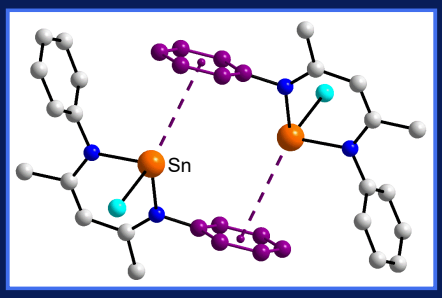
Intermolecular M(lp)···π(arene) interactions



"Menšutkin complexes"

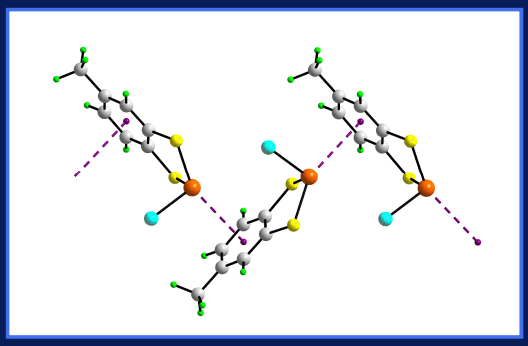


Intermolecular M(lp)···π(arene) interactions



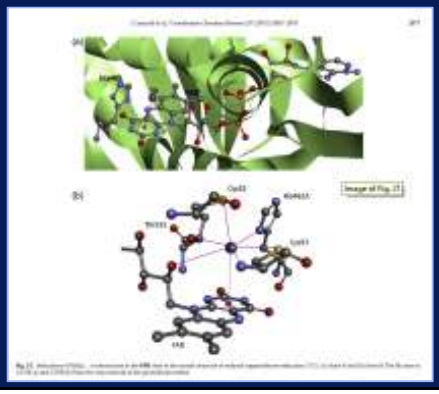
Tin Chemistry: Fundamentals, Frontiers and Applications (2008) Chp. 3

Intermolecular M(lp)···π(arene) interactions



Chem. Commun. **47** (2011) 7608.

Biology?



Energy?

ChemComm

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Cite this: *Chem. Commun.*, 2016, 52, 3500

Received 17th December 2015,
Accepted 27th January 2016

DOI: 10.1039/c5cc10363k

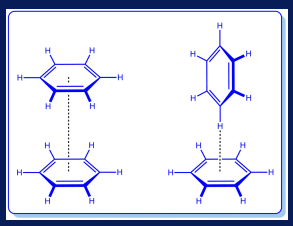
On the nature of the stabilisation of the E···π pnicogen bond in the $SbCl_3$···toluene complex†

Rabindranath Lo,[a] Petr Švec,[b] Zdeňka Růžičková,[b] Aleš Růžička[b] and Pavel Hobza*[ac]

$SbCl_3$ +	C_6H_6	7.7 kcal/mol
	C_6H_5Me	9.6 kcal/mol
	C_6Me_6	15.5 kcal/mol

π-Systems in Supramolecular Chemistry

Classic π-systems/interactions

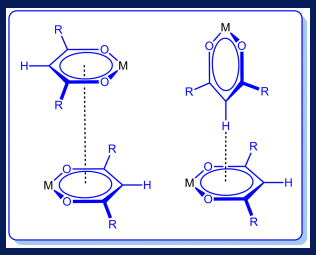


face-to-face edge-to-face

π-Systems in Supramolecular Chemistry

TM Chelate π-systems/interactions

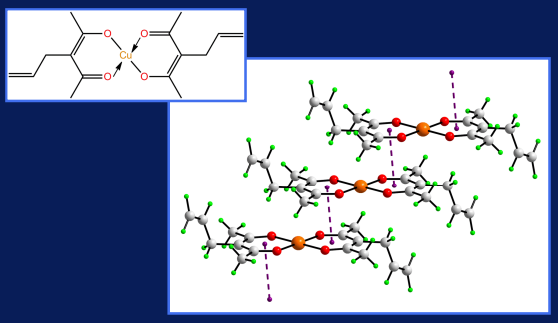
Snezana Zarić



face-to-face edge-to-face

Cryst. Growth Des., 2010, **10**, 3901; *Inorg. Chem.*, 2006, **45**, 4755.

TM π(chelate)···π(chelate) interactions



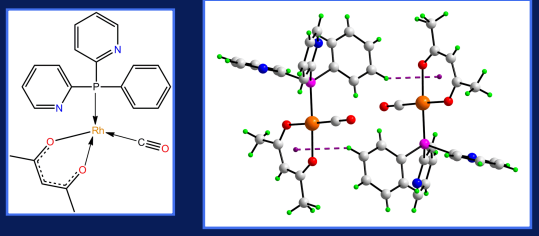
Acta Cryst. C, 1983, **39**, 591.

π(chelate)···π(chelate) interactions

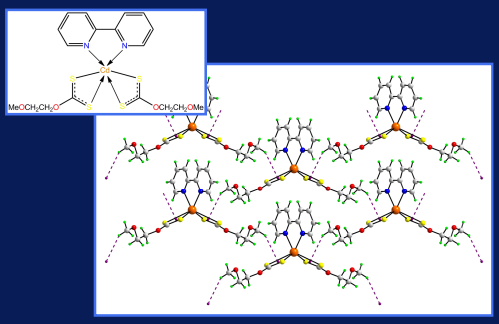
π(chelate)···π(arene) ~ 6 kcal/mol

π(chelate)···π(chelate) ~ 9 kcal/mol

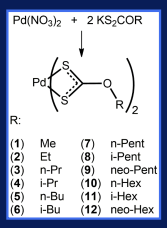
TM arene-H···π(chelate) interactions

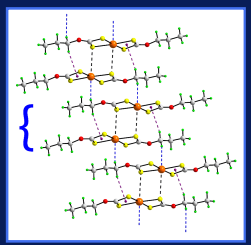


Main group arene-H···π(chelate) interactions

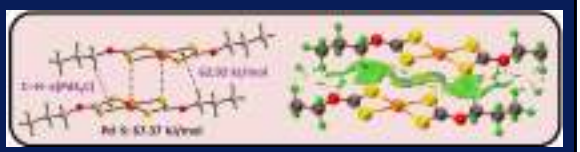


C—H···π(chelate) interactions:





C—H···π(chelate) interactions:



Pd···S 16 kcal/mol
C-H···π(chelate) 15 kcal/mol

Family of Intermolecular Interactions

H-B

Hal-B

6-15 kcal/mol

M···M

M···π

6-15 kcal/mol

up to 12 kcal/mol

M(lp)··· π

C-H··· π(chel)

π(chel)···π

up to15 kcal/mol

up to 15 kcal/mol

up to 9 kcal/mol

"Where are we…"

More to supramolecular life than $(HB)^2$

"Emerging" interactions are competitive

Global molecular packing

www.asca2019.org